REMARKS

The present claim amendments embody the working examples in the specification, which may be summarized as follows.

TABLE 1

		1	2	3	4	5
	Examples	**Unit Dose Concentration Volume**	**Nebulizer/ Compressor**	**Aerosol Output Tl/sec**	**Emitted Dose Efficiency %**	**Duration of Nebulization min**
A	1 and 2	60 mg/ml 5 ml	*Pari LC Plus/ PulmoAide @ 20 psi*	3.8 3.3 (Ex. 2)	26	17.7 20.4 (Ex. 2)
		60 mg/ml 0.5 ml	Aerodose	6.0	68	2.8
		60 mg/ml 1.0 ml	Aerodose	6.4	68	5.2
		60 mg/ml 1.5 ml	AeroDose	6.2	68	8.0
B	3	60 mg/ml 5 ml	*Pari LC Plus/ PulmoAide @ 20 psi*	3.7	'control'	18.1
		120 mg/ml 3.5 ml	Pari LC Plus/ Mobilaire @ 35 psi	6.9	'experimental'	9.7

Notes to Table 1:

A1 and A2. See page 15, lines 1 to 8, and page 65, lines 3 to 7. The control system, *Pari LC Plus/PulmoAide @ 20 psi*, refers to the current conventional delivery system; see page 5, lines 3 to 14, and IDS documents O1 and A.

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1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

A3. Aerosol output is calculated in Tl/sec by dividing the Unit Dose Volume, minus the residual (dead space) volume of the nebulizer, by the Nebulization Time Period. For the Pari LC Plus nebulizer a residual volume of 1 ml is conservatively assumed; see IDS document A at Col. 8, lines 17 to 19, and particularly IDS document O2 at Table 2, row 1. In contrast, the AeroDose nebulizes almost the entire drug dose that is placed in the unit; see the later published IDS document O23 at page 34, right column, second paragraph. Because the AeroDose device is breath actuated, the above-described aerosol output calculation was doubled, on the basis that the aerosolization did not occur during approximately one-half of the duration of nebulization time period.

A4. See page 71, lines 13 to 15.

A5. See page 49, lines 15 to 21.

B1 and B2. See page 75, lines 3 to 13.

B3. See note A3.

B4. For 'control' efficiency see note A4. For 'experimental' see page 92, lines 1 to 7.

B5. See page 92, lines 9 to 16.

Referring to Table 1 above, Example 3 demonstrated that nebulization time for the test 420 mg formulation was substantially reduced below that observed for the marketed 300 mg TOBI® formulation— without changing the pharmokinetics of antibiotic delivery. This study achieved the key benchmark of reduced nebulization time below 10 minutes on the average. (See page 94, lines 7 to 19.)

Thus, Claim 1 has been amended to recite the constellation of parameters, including relatively low unit dose volumes (4.0 ml or less), relatively high unit dose concentrations (about 60 to about 200 mg/ml), and relatively high aerosol outputs (not less than about 4 Tl/sec), requisite to achieve this remarkably short duration of nebulization (less than about 10 minutes).

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206.682.8100

Examples 1 and 2 demonstrated that, moreover, the emitted dose efficiency can be substantially increased without substantial impairment of clinical outcome. Dependent Claims 20 to 23 are directed to such embodiments.

Dependent Claim 27 specifies that at least 20 mg of tobramycin is delivered to the patient, as disclosed at page 71, lines 6-12.

Independent Claim 28 is directed to a preferred embodiment of the present invention.

Thus, by the more efficient administration of tobramycin formulations provided by the claimed invention, substantially smaller volumes of tobramycin than the conventional administration regime are administered in substantially shorter periods of time, thereby reducing the costs of administration and drug wastage, and significantly enhancing the likelihood of patient compliance. (See page 8, line 29, to page 9, line 4.)

INFORMATION DISCLOSURE STATEMENT

The following Table 2 summarizes the disclosures of the documents listed in the contemporaneously filed form PTO-1449.

TABLE 2

IDS Citation No.	**Antibiotics Chemical class generic name**	**Unit Dose Concentration Volume**	**Nebulization Time Minutes**
O1 4/01	Aminoglycoside tobramycin	60 mg/ml 5 ml	~15
O2 2000	Aminoglycoside tobramycin	60 mg/ml 5 ml	7.9-20.9
O3 3/2/00	Aminoglycoside tobramycin	Not reported	≤ 5-10
O4 1999	Aminoglycoside tobramycin	20 mg/ml 4 ml	10.3-18.7

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1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

IDS Citation No.	Antibiotics Chemical class generic name	Unit Dose Concentration Volume	Nebulization Time Minutes
B 1998	Aminoglycosides gentamicin amikacin kanamycin streptomycin neomycin netilmicin tobramycin Macrolide erythromyclamide	4-100 mg/ml 1-5 ml 20 mg/ml 30 ml 60 mg/ml 5 ml	 10-12 10-13
F1	Same as B	Same as B	Same as B
O5 1997			See Fig. 4
O6 1997	Aminoglycoside tobramycin	26.7 mg/ml 3 ml	6-8
O7 1997 Smith	Aminoglycosides tobramycin gentamicin Beta-lactam ceftazidime Quinolone ciprofloxacin Polymoxin colistin	 20, 50, 100, and 200 mg/ml 20 and 40 mg/ml 50, 100, 250, and 500 mg/ml 10 mg/ml 5, 50, and 75 mg/ml	Not reported
O8 1997	Aminoglycoside tobramycin	60 mg/ml 10 ml	≥ 15

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1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

IDS Citation No.	**Antibiotics Chemical class generic name**	**Unit Dose Concentration Volume**	**Nebulization Time Minutes**
U1 1996	Aminoglycoside tobramycin	8-160 mg/ml 1-5 ml 20 mg/ml 30 ml 60 mg/ml 5 ml	 10-12 10-13
F2	Same as U1	Same as U1	Same as U1
O9 1996	Aminoglycoside Tobramycin Polymoxin colistine	 50 mg/ml 1.5-12 ml 11.1 mg/ml 3-12 ml	10 minute sessions
O10 1996	Aminoglycoside tobramycin	20 mg/ml 4 ml 40 mg/ml 2 ml 75 mg/ml 1.1 ml	Not reported
O11 1995 Smith	Aminoglycoside tobramycin	666 ∀ 195 mg	200 inspirations
A ('269) 1994 Smith	Aminoglycosides gentamicin tobramycin	40-100 mg/ml 5 ml	Not reported[1]
O12 1994 Smith	Aminoglycoside tobramycin	20 mg/ml 30 ml 4 ml	Not reported

[1] Attached is a Declaration of Arnold Smith, M.D., which discusses the in vitro "Time to Nebulize" measurements listed in Table 1 of the '269 patent.

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1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

IDS Citation No.	Antibiotics Chemical class generic name	Unit Dose Concentration Volume	Nebulization Time Minutes
O13 1994	Aminoglycoside tobramycin	7.5 mg/kg/dose mean = 266 mg	60
O14 1993	Aminoglycosides gentamicin tobramycin amikacin neomycin Polymoxin colistin Beta-lactams ceftazidime carbenicillin ticarcillin cephaloridine cloxacillin methicillin *Antifungal* amphotericin	4 ml 40-160 mg 40-160 mg 250-500 mg 0.5-1 mg 10 mg	10-20
O15 Le Conte 1993	Aminoglycoside tobramycin	150 mg/ml 2 ml	~5
O16 1993 Smith	Aminoglycoside tobramycin	50 mg/ml 30 ml	200 tidal inspirations
O17 1993	Aminoglycoside tobramycin	0.35 mg/ml 2 ml	10-minute sessions (to guinea pigs)
O18 1991	Aminoglycoside tobramycin	10 mg/ml	15 (to rats)
O19 1989 Smith	Aminoglycoside tobramycin	20 mg/ml 30 ml	200 inhalations
O20 1989	Aminoglycoside tobramycin	40 mg/ml 2 ml	≥ 15
O21 1989	Aminoglycoside tobramycin	80 mg 2 ml	Not reported
O22 1988	Adrenergic agents (for asthma)	≤ 0.3 ml of 0.5 % solution 0.5 % solution	15- 20 minutes 5 inspirations

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Seattle, Washington 98101
206.682.8100

Referring to the above Table 2, several of the listed documents disclose nebulization times of about 10 minutes or less, but none read on the constellation of parameters recited in the present claims, as summarized below.

O2 evaluated the standard 5 ml tobramycin, 60 mg/ml, with the Pari LC Plus nebulizer using various compressors. Table 2 indicates that the faster compressors (Nebulization time) were less efficient (Residual volume) that the standard PulmoAide compressor.

O3 simply discloses a goal to reduce Tobi's delivery time of 15 to 20 minutes to 5 to 10 minutes or less.

O4 discloses a relatively dilute tobramycin solution of 20 mg/ml.

B discloses, in Table 3, delivery of 5 ml erythromyclamide, 60 mg/ml, in 10 minutes using the Pari LC nebulizer with the PulmoAide compressor.

O6 discloses a relatively dilute tobramycin solution of 26.7 mg/ml.

U1 discloses, in Table 3, delivery of 5 ml tobramycin, 60 mg/ml, in 10 minutes using the Pari LC nebulizer with the PulmoAide compressor.

O14 discloses that a high flow rate reduces the nebulization time and 10-20 minutes is suggested as a clinically acceptable range; see page 101, right column.

O15 discloses nebulized delivery of 2 ml tobramycin, 150 mg/ml, to healthy volunteers in

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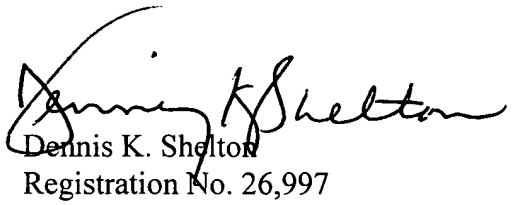
Suite 2800
Seattle, Washington 98101
206.682.8100

about 5 minutes. However, the emitted dose efficiency was only 17 percent (page 1281, left column), and lung uptake of the antibiotic was reportedly poor (page 1281, right column).

Respectfully submitted,

CHRISTENSEN O'CONNOR
JOHNSON KINDNESS[PLLC]



Dennis K. Shelton
Registration No. 26,997
Direct Dial No. 206.695.1718

TFB:snh

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS[PLLC]
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100